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54. Name of Invention: Coagulation inhibitor and lipo-clearer

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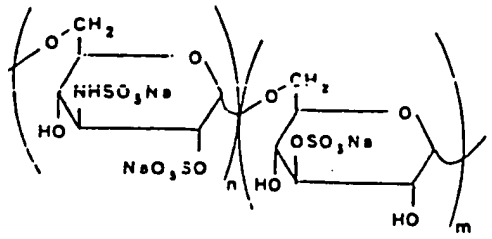
Specifications

1. Name of the invention

Coagulation inhibitor and lipo-clearer

2. Claim

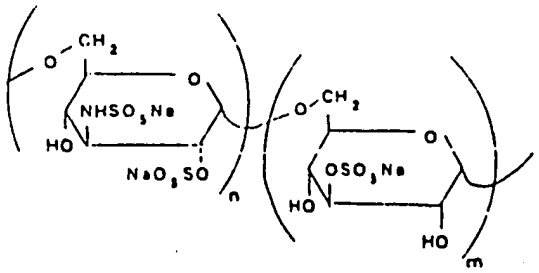
(1) This coagulation inhibitor and lipo-clearer is characterized by containing an active component of sulfated polysaccharide shown in the following equation.



(In the equation, m/n is 0 - 5, m+n is 30 - 150 integer)

3. Detailed specifications

The invention is a coagulation inhibitor and lipo-clearer characterized by containing an active ingredient of sulfated polysaccharide shown in the following equation.

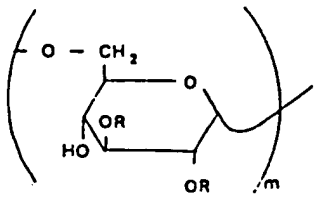


(In the equation, m/n is 0 - 5, m+n is 30 - 150 integer)

Thrombosis or lipemia often accompany illnesses like malignant tumors, arteriosclerosis, diabetes, and nephrotic syndrome. Recently, along with an increase in the above illnesses, thrombosis and lipemia show a trend of increasing.

Currently, drugs useful for treatment of these illnesses, for example, are dextran sulfate or heparin. In other words, dextran sulfate is an ester sulfate of dextran, a polymer of D-glucopyranose combined with α-1,6 produced by a microorganism such as Leuconostoc mesenteroides, has a lipo-clearing action and decreases the cholesterol and triglyceride in the blood. Moreover, it is a coagulation inhibitor, an anti-hyaluronidase and a cellulose solvent. It is known to be an effective drug for treating thrombosis, high lipemia, and arteriosclerosis.

These physiological activities are stronger the higher the molecular weight and sulfur content, but at the same time, toxicity increases.

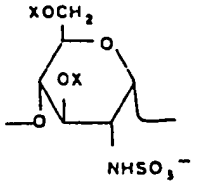


R=H : dextran

R=SO_3Na : dextran sulfate

On the other hand, heparin, a muco-polysaccharide existing in animal tissue, has a wide range of physiological functions like strong coagulation inhibition and lipo-clearing. These functions are very strong compared to man-made heparinoid, but the quality of the standard product is not uniform, and since the structure is complex, the isolation

process is also complicated. Heparin is characterized by containing sulfated amino-sugar in the molecules, for example the unit below.

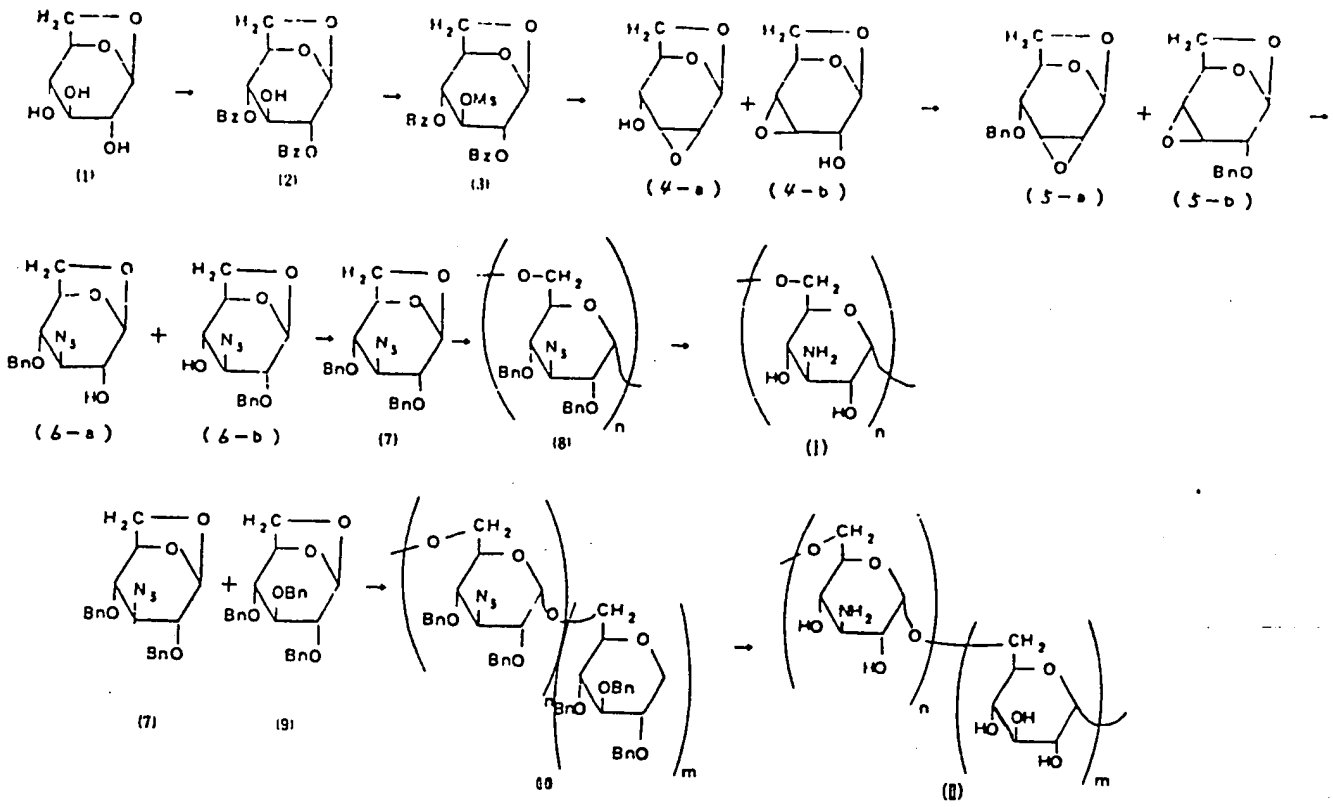


(x shows H or SO_3^- in the equation)

The inventors diligently conducted research with the objective of synthesizing a coagulation inhibitor and lipo-clearer. As a result, they succeeded in synthesizing a new sulfated polysaccharide not naturally occurring and containing an amino group as in heparin in the molecules and a sugar chain combined with α-1,6 as shown in the above equation. This sulfated polysaccharide appears to have superior coagulation inhibition and lipo-clearing as in the following operation examples, resulting in the completion of the invention.

The invention's active component is explained below.

The active component of the invention is sulfated polysaccharide as shown in the above equations and can be synthesized by the following process. First the inventors succeeded in synthesizing a copolymer of D-glucose and an amino-sugar polymer with a high degree of polymerization including an amino group similar to that of heparin and a sugar chain combined with α-1,6 by using an azide sugar as a precursor of the amino-sugar. (see patents 57-180603, 57-180604, 57-180605, and 57-180606)



(In the equation, Bz is benzoyl group, Ms is methanesulfonyl group, Bn and m are the same as in earlier equations.)

In other words, compound (2) is easily attained by treating 1,6-anhydro-β-D-glucopyranose (1) derived from β-D-glucopyranose with benzoylchloride (M. Cerny et al., Collection Czechoslov, Chem. Commun., Vol. 26, 2542 (1961)).

Compound (2) is dissolved in dry pyridine and frozen. As it is agitated, methanesulfonylchloride is dripped in and gradually rises to room temperature. After 3 hours, when opened in a large amount of ice water and agitated, coarse crystals of compound (3) are extracted. After separation(?), rinsing, and drying, it is recrystallized from methanol, producing white crystals of compound (3).

Compound (3) is dissolved in chloroform and frozen. Sodium methoxide solution prepared by dissolving metallic sodium in methanol is dripped into this during agitation. After the mixture sits at room temperature overnight, it is neutralized in 5% hydrochloric acid, and vacuum concentration hardened. The residue is 5 times extracted

in acetone. When the extracted solution is vacuum concentrated, an oily material is produced. When this is refined by silica gel chromatography (solvent used chloroform-methanol, 100:1 v/v), a mixture of compounds (4-a) and (4-b) is produced.

The mixture of compounds (4-a) and (4-b) is dissolved in dry tetrahydrofuran, frozen sodium hydride (60% purity) is added and agitated for 30 minutes. Then benzyl bromide is added and reacted at room temperature for four hours. After adding saturated ammonium chloride and agitating for 30 minutes, it is 3 times extracted in ethyl. After the sampled solution is dried in magnesium sulfate anhydride, it is vacuum concentrated; when the oily material produced is refined by silica gel chromatography (solvent used benzene-ethyl acetate, 20:1 v/v), a mixture of oily compounds (5-a) and (5-b) is produced.

The mixture of compounds (5-a) and (5-b) is dissolved in a mixed solvent of ethanol and saturated ammonium chloride water, sodium azide is added and agitated 60 hours, and heat refluxed. After it cools, distilled water is added, the ethanol is vacuum removed, the remaining aqueous solution is extracted in chloroform. After drying the extracted solution in magnesium sulfate anhydride, it is vacuum concentrated, producing an oily material. When it is refined by silica gel chromatography (solvent used benzene-ethyl, 20:1 v/v), a mixture of compounds (6-a) and (6-b) is produced.

The mixture of compounds (6-a) and (6-b) is dissolved in dry tetrahydrofuran and frozen. After sodium hydride (60% purity) is added and agitated for 30 minutes, benzyl bromide is added. After being agitated for 3 hours at room temperature, frozen saturated ammonium chloride aqueous solution is added and agitated for another 30 minutes. This mixed solution is extracted in ethyl, after the extracted solution is dried in magnesium sulfate anhydride and vacuum concentrated, an oily material is produced. When it is refined by silica gel chromatography (solvent used hexane-ethyl sulfate, 5:1 v/v), oily compound (7) is produced. This is let sit, crystallizes, and can be recrystallized from cyclohexane.

Compound (7) is vacuum dried overnight under a high vacuum of 10^{-5} mmHg, then dissolved in methylene chloride previously dried by calcium hydride in a vacuum ampule. After this solution is mixed at -60°C with phosphorous pentafluoride, benzoyl

fluoride, and methylene chloride previously reacted for 30 minutes in a polymerized vessel, and then reacted for 23 hours at -60°C, the polymerized ampule is opened and methanol is poured in. At this time, since the polymer precipitates, chloroform is added until the polymer is sufficiently dissolved; it is then neutralized in a aqueous solution of sodium bicarbonate, rinsed, and dried in sodium sulfate anhydride. After the drying agent is separation(?) removed, the separated(?) solution is concentrated, petroleum benzine is added and it is reprecipitated. It is not twice more dissolved, concentrated, and reprecipitated, then dissolved in benzene. It is not freeze dried, producing polymer (8).

By changing the amount used and the polymerization time of compound (7) and conducting the above reactions under the same conditions, polymers with a variety of molecular weights and degrees of polymerization can be produced.

By reducing this with the following methods, amino polysaccharide (I) is produced.

The reduction of polymer (8) is by batch reduction, in other words, by alkali metals in liquid ammonia. The alkali metals can be potassium, sodium, or lithium. As it is necessary for the alkali metals to add over 6 atoms per one unit in the polymer, it is usually desirable to have 3 times the weight. Polymer (8) is added previously dissolved in a suitable solvent, for example, 1,2-dimethoxyethane or diglime.

A suitable reaction temperature is from nearly -70° to -80°C, a suitable reaction time is from nearly 30 minutes to 3 hours.

In other words, metallic sodium and liquid ammonia are mixed and held at -78°C, the 1,-dimethoxyethane solution of polymer (8) is gradually dripped in. It is necessary for the 1,2-dimethoxyethane to be previously dried sufficiently in metallic sodium. At the time of reaction, it is good to agitate the system so that it becomes uniform. After the reaction of the prescribed time, the reaction is stopped by adding ethanol or ammonium chloride, a small amount of water is added, it is let stand overnight, and the ammonia evaporates. The unreacted polymer is extracted in methylene chloride and removed. It is dialyzed for 3 days in distilled water, after separating(?) any insoluble parts, the insoluble portion is vacuum dried, and by concentrating and freeze-drying the soluble portion, amino polysaccharide (I) is produced.

On the other hand, compound (9) can be easily produced by treating 1,6-anhydro-β-D-glucopyranose (I) with benzyl bromide.

Copolymerizing and reducing compounds (7) and (9) by the following methods will produce an amino-sugar copolymer (II).

The copolymerization reaction is by dissolving compounds (7) and (9) in a sufficiently dried solvent and reacting them with Lewis acid as a catalyst. The solvent can be methylene chloride or chloroform. The Lewis acid can be phosphorous pentafluoride, antimony pentachloride, or boron trifluoride ethylate, but phosphorous pentafluoride is best with respect to yield and solid regularity of the attained copolymer. The amount of Lewis acid used can be 2 - 7 mole% for the total mole number of compounds (7) and (9), but 2 - 3 mole% is especially suitable. Moreover, by changing the mix ratio of compounds (7) and (9), various copolymers can be produced.

Reaction temperature can be from nearly -30 - -60°C and polymerization time can be from nearly 40 - 60 hours.

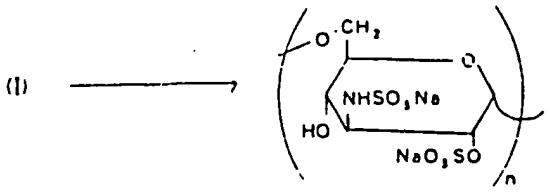
It is beneficial to conduct the polymerization reaction in a vacuum or in an inert gas atmosphere (for example N_2 gas).

Thus, in the molecule, a polysaccharide (10) containing an azide sugar and an azide group is produced, and the amino-sugar copolymer (II) is produced by then batch reducing this under the same conditions as above.

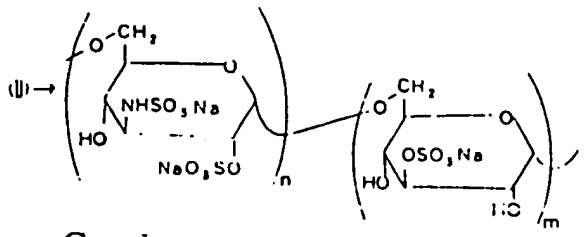
Thereby, the active component of the invention, sulfated polysaccharide, is produced by the following reaction of the produced polymers (I) and (II).

After the above polymers (I) and (II) are pretreated and swelled, they are suspended in a suitable solvent. The solvent can be pyridine, dimethylsulfoxide, or dimethylformaamide. This suspended solution is reacted with a sulfated agent (and the above solvent). The sulfated agent can be chlorosulfon acid, or piperidine-N-sulfuric acid. The amount of the sulfated agent used is 20 - 30 moles for the initial material, amino monosaccharide residue. Reaction time and reaction temperature are different for the solvent and sulfated agent, but 70 - 100°C and 45 - 60 minutes are suitable. After the reaction, it cools and distilled water is added, stopping the reaction. Then it is neutralized by an alkali such as sodium hydroxide, ethanol is added, and the polymer is

precipitated. This is centrifugated and dissolved in distilled water. After dialysis, by concentration drying, the active component, sulfated polysaccharide, is produced.



Homopolymer (III)



Copolymer (IV)

(but, in the equation m,n mean the same as before)

The active component of the invention can be produced as above, but in the case of homopolymer (III), the limiting viscosity should be from 0.15 to 0.18, sulfur content should be 16 - 18%. In the case of copolymer (IV), limiting viscosity should be 0.07 - 0.10, sulfur content should be 10 - 15%. The invention, in accordance to clinical diseases, can be administered in the most appropriate dosage method. In other words, by intravenous injection, subcutaneous injection, muscular injection, or oral dosage, but intravenous dosage is appropriate for acute diseases.

Furthermore, the active component of the invention is dissolved or suspended in an appropriate inert solvent such as sterile water or physiological saline solution, or an inert carrier or filler is added, for example it is suitable to use drug forms like non-oral forms which are injected and powder, granulated, capsule, pills, coating, shirappu (transliterated), liquid and other oral drugs.

The above inert carrier or filler can be calcium phosphate, calcium carbonate, glucose, lactose, sucrose, dextrine, cane sugar nester, starch, sorbitol, mannite, crystallized cellulose, talc, kaolin, synthetic aluminum silicate, carboxymethylcellulose, methylcellulose, cellulose acetate phthalate, polyvinyl pyrolidone, polyvinylalcohol, arabia gum, traganth gum, gelatin, agar powder, or shellac.

Usually, the active component of the invention, based on the composite weight, should contain 1 - 90 weight%. The content can change appropriately for the drug form.

Below, the invention, production examples, operation examples, and experimental

examples are described, but the invention is not limited to these.

Production Example 1

Polymer (1-a) ($\bar{M}n=3.5\times10^4$, $\bar{\bar{D}}Pn=95$(100 mg, NH_2 group:0.62 mmol, OH group:1.24 mmol) is pulverized in water (10 ml) and is centrifugated. Then, in 20 ml ethyl, it is 3 times agitation centrifugated and is suspended in 8 ml previously dried pyridine. This suspended solution and chlorosulfon acid, (1 ml, 15 mmol) previously reacted at 0°C, are added to 6 ml dry pyridine, soaked in boiling water, and reacted for one hour. After it cools, 20 ml of distilled water is added and the reaction stops. It is neutralized by 2.5 N sodium hydroxide aqueous solution (7.5 ml), ethanol (50 ml) is added, the polymer is precipitated. This is centrifugated and dissolved in distilled water, after it is dialyzed for 3 days, sulfated amino polysaccharide homopolymer (IV-a) is produced by concentration and freeze drying. (183.7 mg, 81.0%)

[Physical properties of homopolymer (III-a)]

		C	H	H	S
Ultimate analysis value	observed value	20.16	4.18	3.75	16.14
	Calculated value ($C_6H_9O_{10}NS_2Na_2$)	19.73	2.48	3.83	17.56

ninhydrin reaction: negative

IR: 580 cm^{-1} (M)
800 cm^{-1} (M)
610 cm^{-1} (M)
1240 cm^{-1} (S, broad)
1510 cm^{-1} (M)

^{13}C-NMR: δ97.53 ppm (1C, C-1)
75.54
74.68 (3C, C-2, C-4, C-5)
71.03
68.07 (1C, C-6)
55.07 (1C, C-3)

$[\alpha]_D^{25}$+116.9° (C=1.0, $CHCl_3$)

$[\eta]$=0.17 (in H_2O, 30°C)

Production Example 2

Polymer (II-a) ($\bar{\bar{D}}Pn=144$, m/n=1.04, 100 mg) is dissolved in water (2 ml), and ethanol 20 ml is added and it is precipitated. After centrifugal separation and agitation separation in ethanol, then ethyl, it is suspended in previously dried pyridine (8 ml).

This suspended solution and chlorosulfon acid, (1 ml, 15 mmol) previously reacted at 0°C, are added to dry pyridine (6 ml), soaked in boiling water, and reacted for 1 hour. After cooling, distilled water (20 ml) is added and the reaction stops. It is neutralized in 2.5 N sodium hydroxide aqueous solution (7.5 ml), ethanol (50 ml) is added, and the polymer is precipitated. This is centrifugated and dissolved in distilled water. After 3 days of dialysis, a sulfated polysaccharide containing an amino-sugar [copolymer (IV-a)] is produced. (168 mg, 76.2%)

[Physical properties of copolymer (IV-a)]

	C	H	H	S
Ultimate analysis value : observed value	17.40	3.39	1.55	14.65
Calculated value $C_6H_{8.589}O_{10.211}N_{0.489}S_{1.90}Na_{1.90}\cdot 3H2O$	17.59	3.59	1.68	14.87

(sulfation rate: per sugar-residue SO_3^- 1.90 units)
IR: 580 cm^{-1} (M)
800 cm^{-1} (M)
1240 cm^{-1} (s, broad)
1510 cm^{-1} (W)
$[\alpha]_D^{25}$=+100.2° (C=1.0, H_2O)
$[\eta]$=0.07 (in H_2O, 30°C)

Production Example 3

Other than using copolymer (II-b) ($\bar{O}\bar{P}n$=100 - 120, m/n=4.76, NH_2 group 0.114 mmol, OH group 1.74 mmol, 100 mg), if the same reaction and post treatment as in Production Example 2 are conducted, a sulfated polysaccharide containing an amino-sugar (IV-b) is produced. (176 mg, 72.0%)

[Physical properties of copolymer (IV-b)]

	C	H	H	S
Ultimate analysis value : observed value	22.76	4.46	0.67	10.82
Calculated value $C_6H_{9.115}O_{8.025}N_{0.185}S_{1.07}Na_{1.07}$	22.16	4.68	0.80	10.55

(sulfation rate: per sugar-residue SO_3^- 1.07 units)
IR: 580 cm^{-1} (M)
800 cm^{-1} (M)
1240 cm^{-1} (s, broad)
$[\alpha]_D^{25}$=+109.6° (C=1.0, H_2O)
$[\eta]$=0.07 (in H_2O, 30°C)

Operation Example 1 (Injection form)

After 5 g of the sulfated polysaccharide produced in Production Example 1, 0.2 g sodium bicarbonate, and 0.4 g sodium chloride are dissolved in distilled water, for injection, to make 100 ml, it is made an injectable drug by the usual method.

Operation Example 2 (Tablet form)

After 200 g of the sulfated polysaccharide produced in Production Example 2 and 140 g lactose are mixed, it is passed through a US standard screen (60 mesh). Then after the mixture is dampened in 40 g alcoholic polyvinylpyrolidone, it is passed through a 12 mesh screen, granulated, and dried. After the dried granules are passed through 16 mesh screen, 50 g talc and 20 g starch are added, then a tablet massing 450 mg is prepared.

Operation Example 3 (Granulated form)

200 g of the sulfated polysaccharide produced in Production Example 3, 150 g methyl cellulose, 80 g cornstarch, and some seasonings are mixed and passed through 60 mesh screen. After the mixture is moistened by 20 g alcoholic polyvinyl pyrolidone, it is granulated in a stainless steel mesh with a 0.7 mm diameter.

Experimental Example 1 (Coagulation inhibition)

It is measured corresponding to the strength examination method for heparin of the Pharmacopeia of the United States of America (XIX, items 229 - 230). (However, instead of sheep blood plasma, cow blood plasma is used.)

Experimental material is dissolved in physiological saline solution, the concentration is 160 γ/ml. Also a 10 γ/ml physiological saline solution of standard heparin (160 IU/mg) is prepared.

A solution of the experimental material and a standard heparin solution are respectively 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, and 0.05 ml each placed in glass vessels (13×105 mm), then a physiological saline solution is added and mixed so the total volume becomes 0.8 ml.

In each vessel, cow blood plasma*/ml is added and mixed, then 2% calcium chloride aqueous solution 0.2 ml is added, immediately the vessel is gently inverted and mixed and kept in a 37°C water bath.

After 30 minutes, the blood clot condition in each vessel is classified into classes of 0, 0.25, 0.5, 0.75, and 1.0. The strength of the experimental material was determined from the volume of the experimental material and the standard heparin when the clotting condition was 0.5. These results are shown in Table 1.

*Cow blood plasma: previously, in a syringe a 10% sodium citrate ($Na_5C_6H_2O_7 \cdot 2H_2O$) aqueous solution 40 ml is added, 960 ml fresh cow blood is added to this syringe, after mixing and centrifugal separation at 3000 rpm for 10 minutes, blood plasma is removed.

Table 1 Coagulation inhibition

Experimental material	Coagulation inhibition (U/mg)
Homopolymer (III-a)	15.9
Copolymer (IV-a)	15.9
Copolymer (IV-b)	17.2
Dextran sulfate[a)]	6.4

a) control, limiting viscosity $[\eta]$ 0.0256; S content 18.4%

The drug form of the invention has nearly 10% of the coagulation inhibition of heparin and 2.5 times that of the control, dextran sulfate.

Experimental Example 2 (Overall coagulation inhibition)

Using Japanese white rabbits (male) weighing 2.5 - 3.0 kg, an experimental material (2.5% physiological saline solution) is injected at 25 mg/Kg. After 10 minutes, blood is taken from the ear vein, blood clotting time is measured by the Lee White variation method (Kanei et al., Summary of Clinical Experimentation Methods, Kanebara Shuppan K.K., 1978, Vol. 28).

In other words, 2 dried glass experimental vessels (10×120 mm) are kept in a 37°C fixed temperature water tank, after taking the blood, immediately the injection needle is

undone, 1 ml is added so it won't froth.

After the first vessel is let stand 5 minutes, every 30 seconds, diagonally brought down and checked for blood clots. If there are clots, the second vessel is observed under the same conditions.

The time from when the blood solution enters the syringe from the vein until the clots form in vessel 2 is the total blood clotting time. These results are shown in Table 2.

Table 2 Total blood clotting time

Experimental material	Total blood clotting time	
	before dosage	10 minutes after dosage
Homopolymer (III-a)	6 minutes	over 60 minutes
Copolymer (IV-a)	9 minutes	over 60 minutes
Copolymer (IV-b)	9 minutes	over 60 minutes
Dextran sulfate[a)]	10 minutes	over 60 minutes

a) control, limiting viscosity $[\eta]$ 0.0256; S content 18.4%

The active components of the injection, with a 25 mg/Kg dosage, significantly prolong blood solution clotting time.

Experimental Example 3 (Lipo-clearing action)

Using Japanese white rabbits (male) weighing 2.5 - 3.0 Kg, the experimental materials (0.5% physiological saline solution) were injected at 5 mg/Kg. 10 minutes later, from the ear vein, blood was removed and the lipo-clearing action is measured by the Hara·Kuzudani method (Protein, Nucleic acid, Oxygen, 10, 1224 - 1229, 1965).

In other words, into a syringe in which 0.1 ml of a 10% sodium citrate aqueous solution was placed previously, 2.4 ml whole blood was drawn, it was centrifugated at 3000 rpm for 5 minutes, producing blood plasma.

Separately, 550 mg cow albumen was dissolved in 8.5 ml phosphoric acid buffered solution with pH 7.4, then 1.5 ml of 10 times (??) emulsion Ediol (from Calbiochem co.) is added, producing a substrate solution.

1 ml blood plasma and 1 ml substrate solution are mixed, immediately in 5 mm layer length, wavelength 660 nm extinction degree ($-\log T_1$) is measured.

Then, after 3 hours incubation in a fixed temperature bath at 37°C, under the same conditions extinction rate ($-\log T_2$) was measured.

On the other hand, using blood plasma previously dosed with the experimental materials as a control, the extinction degrees ($-\log T_3$ and $-\log T_4$) are measured before and after the incubation.

From the following equation, the lipo-clearing action of the experimental materials is found.

Lipo-clearing action $= \{(-\log T_1)-(-\log T_2)\}-\{(-\log T_3)-(-\log T_4)\}$
(Δ-logT)

Table 3 Lipo-clearing action (Δ-logT)

Experimental material	Lipo-clearing action
Homopolymer (III-a)	0.759
Copolymer (IV-a)	0.764
Copolymer (IV-b)	0.773
Dextran sulfate[a)]	0.549

a) control, limiting viscosity [η] 0.0256; S content 18.4%

The active ingredient of the invention has superior lipo-clearing action.

Moreover, acute toxicity (LD_{50}) using mice and rates in the active component compounds respectively was over 3 g/Kg and over 2 g/Kg (injection).

Conclusion

The active component of the inventions, as is clear from the above Operation Examples, has coagulation inhibition or lipo-clearing action superior to dextran sulfate, also acute toxicity (LD_{50}) was over 3 g/Kg (Mice) and over 2 g/Kg (rats), so it is anticipated that its use as a drug will be very promising.